



## **Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents**

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## Epidemiology

Isosporiasis, also known as cystoisosporiasis, occurs worldwide but predominantly in tropical and subtropical regions. Immunocompromised patients, including those who are HIV-infected, are at increased risk for chronic, debilitating illness.<sup>1-7</sup> Although *Isospora* (*Cystoisospora*) *belli* completes its life cycle in humans, the oocysts shed in the feces of infected individuals must mature (sporulate) outside the host, in the environment, to become infective. On the basis of limited data, the maturation process is completed in approximately 1 to 2 days but might occur more rapidly in some settings.<sup>2</sup> Infection results from ingestion of sporulated oocysts, such as from contaminated food or water. After ingestion, the parasite invades enterocytes in the small intestine. Ultimately, immature oocysts are produced and shed in stool.

## Clinical Manifestations

The most common manifestation is watery, non-bloody diarrhea, which may be associated with abdominal pain, cramping, anorexia, nausea, vomiting, and low-grade fever. The diarrhea can be profuse and prolonged, particularly in immunocompromised patients, resulting in severe dehydration, electrolyte abnormalities such as hypokalemia, weight loss, and malabsorption.<sup>6-12</sup> Acalculous cholecystitis/cholangiopathy<sup>2,13-15</sup> and reactive arthritis<sup>16</sup> also have been reported.

## Diagnosis

Typically, infection is diagnosed by detecting *Isospora* oocysts (dimensions, 23–36  $\mu\text{m}$  by 12–17  $\mu\text{m}$ ) in fecal specimens.<sup>2</sup> Oocysts may be shed intermittently and at low levels, even by patients with profuse diarrhea. Diagnosis can be facilitated by repeated stool examinations with sensitive methods, such as modified acid-fast techniques, on which oocysts stain bright red, and UV fluorescence microscopy, under which they autofluoresce.<sup>2,17</sup> Infection also can be diagnosed by detecting oocysts in duodenal aspirates/mucus or developmental stages of the parasite in intestinal biopsy specimens.<sup>2,10</sup> Extraintestinal infection, such as in the biliary tract, lymph nodes, spleen, and liver, has been documented in postmortem examinations of HIV-infected patients.<sup>2,18-20</sup>

## Preventing Exposure

Because *I. belli* is acquired by ingesting infected water or food, avoiding potentially contaminated food or water in isosporiasis-endemic areas may help prevent infection.

## Preventing Disease

In some settings, chemoprophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX) has been associated with a lower incidence or prevalence of isosporiasis.<sup>1,3,4,21</sup> In a randomized, placebo-controlled trial, daily TMP-SMX (160/800 mg) was protective against isosporiasis in persons with early-stage HIV infection (World Health Organization clinical stage 2 or 3 at enrollment).<sup>1</sup> In an observational study, incidence of isosporiasis decreased after widespread introduction of antiretroviral therapy (ART), except in patients with CD4 counts <50 cells/mm<sup>3</sup>.<sup>3</sup> After adjustment for the CD4 T lymphocyte (CD4) cell count, the risk of isosporiasis was substantially lower in those receiving prophylaxis with TMP-SMX, sulfadiazine, or pyrimethamine (unspecified regimens). In analyses of data from a Los Angeles county AIDS surveillance registry during the pre-ART era, the prevalence of isosporiasis was lower in patients with versus without a history of *Pneumocystis pneumonia*—indirect evidence of a protective effect from use of TMP-SMX for *Pneumocystis pneumonia*.<sup>4</sup> Insufficient evidence is available, however, to support a general recommendation for primary prophylaxis for isosporiasis per se, especially for U.S. travelers in isosporiasis-endemic areas.

## Treating Disease

Clinical management includes fluid and electrolyte support for dehydrated patients and nutritional supplementation for malnourished patients (**AIII**). TMP-SMX is the antimicrobial agent of choice for treatment of isosporiasis (**AI**). It is the only agent whose use is supported by substantial published data and clinical experience. Therefore, potential alternative therapies should be reserved for patients with documented sulfa intolerance or in whom treatment fails (**AIII**).

Three studies in HIV-infected patients in Haiti have demonstrated the effectiveness of various treatment regimens of TMP-SMX.<sup>6,7,22</sup> The patients were not receiving ART, and laboratory indicators of immunodeficiency (such as CD4 cell counts) were not specified. On the basis of the initial studies,<sup>6,7</sup> the traditional treatment regimen has been a 10-day course of TMP-SMX (160/800 mg) administered orally four times daily (**AI**).<sup>23</sup> In another study, TMP-SMX (160/800 mg) administered twice daily was also effective (**BI**).<sup>22</sup> Although published experience using two daily doses of TMP-SMX (160/800 mg) is limited, one approach would be to start with this regimen but to increase the daily dose and the duration of therapy (up to 3–4 weeks)<sup>6,10</sup> if symptoms worsen or persist (**BIII**). Intravenous administration of TMP-SMX should be considered for patients with potential or documented malabsorption.

Limited data suggest that therapy with pyrimethamine–sulfadiazine and pyrimethamine–sulfadoxine may be effective.<sup>2,9,10,24–26</sup> However, the combination of pyrimethamine plus sulfadoxine is not typically recommended for use in the United States (**CIII**); it has been associated with an increased risk of severe cutaneous reactions, including Stevens-Johnson syndrome,<sup>27</sup> and pyrimethamine and sulfadoxine clear slowly from the body after therapy is discontinued.

Single-agent therapy with pyrimethamine has been used, with anecdotal success for treatment and prevention of isosporiasis.<sup>3,28,29</sup> Pyrimethamine (50–75 mg/day) plus leucovorin (10–25 mg/day) to prevent myelosuppression may be an effective treatment alternative; it is the option for sulfa-intolerant patients (**BIII**).

The author panel has issued a statement on the availability of pyrimethamine. For more information, please visit <https://aidsinfo.nih.gov/news/1604/notice-of-availability-of-pyrimethamine>.

## Special Considerations with Regard to Starting ART

Only limited data address the utility of ART in the setting of *Isospora* and HIV co-infection.<sup>3,14,21</sup> Immune reconstitution with ART may result in fewer relapses of isosporiasis, and no cases of immune reconstitution inflammatory syndrome (IRIS) have been reported. Therefore, the potential benefits of ART likely outweigh the risks. For patients with isosporiasis who otherwise fulfill criteria for ART, TMP-SMX therapy and ART can be started simultaneously; there is no known reason to defer initiation of ART other than the potential for poor ART absorption (**AIII**).

## Monitoring of Response to Therapy and Adverse Events (Including IRIS)

Patients should be monitored for clinical response and adverse events. In HIV-infected patients, TMP-SMX therapy is commonly associated with side effects, such as rash, fever, leukopenia, thrombocytopenia, and elevated transaminase levels. IRIS has not been described.

## Managing Treatment Failure

If symptoms worsen or persist despite approximately 5 to 7 days of TMP-SMX therapy, the possibilities of noncompliance, malabsorption, and concurrent infections/enteropathies should be considered; the TMP-SMX regimen (daily dose, duration, and mode of administration) also should be reevaluated. For patients with documented sulfa intolerance or in whom treatment fails, use of a potential alternative agent (typically pyrimethamine) should be considered. Ciprofloxacin is a second-line agent (**CI**). On the basis of limited data from a randomized, controlled trial in Haiti, ciprofloxacin (500 mg twice daily for 7 days) is less effective than TMP-SMX but may have modest activity against *I. belli*.<sup>22</sup>

Unsubstantiated or mixed data are available for albendazole,<sup>29-31</sup> nitazoxanide,<sup>32,33</sup> doxycycline,<sup>34</sup> the macrolides roxithromycin and spiramycin,<sup>25,35,36</sup> and the veterinary anticoccidial agent diclazuril (**CIII**).<sup>37,38</sup> Limited data suggest that drugs such as metronidazole, quinacrine, iodoquinol, paromomycin, and furazolidone are ineffective.<sup>8,25,26,28,35,37</sup> Apparent or partial responses, if noted, may be attributable to treatment of concomitant infections or to nonspecific effects.

## Preventing Recurrence

Patients with CD4 cell counts <200 cells/mm<sup>3</sup> should receive secondary prophylaxis (chronic maintenance therapy) with TMP-SMX, which is also protective against *Pneumocystis jirovecii* and *Toxoplasma gondii* infections (**AI**). In studies in Haiti, approximately 50% of patients who did not receive secondary prophylaxis had symptomatic recurrences approximately 2 months after completing a course of TMP-SMX therapy, relapses rapidly responded to retreatment, and secondary prophylaxis decreased the risk of relapse.<sup>6,7,22</sup> In a randomized, placebo-controlled trial, no symptomatic recurrences were noted in patients who received maintenance therapy with thrice-weekly TMP-SMX (160/800 mg) (**AI**).<sup>7</sup> Daily TMP-SMX (160/800 mg) and thrice-weekly TMP-SMX (320/1600 mg) have been effective (**BIII**);<sup>5,10</sup> however, clinical and parasitologic relapses despite maintenance TMP-SMX therapy and ART have been reported.<sup>14</sup>

In sulfa-intolerant patients, pyrimethamine (25 mg/day) with leucovorin (5–10 mg/day) has been used (**BIII**).<sup>28</sup> On the basis of limited data, ciprofloxacin (500 mg thrice weekly) is considered a second-line alternative (**CI**).<sup>22</sup>

## When To Stop Secondary Prophylaxis

The issue of discontinuing prophylaxis has not been evaluated in a clinical trial. Chemoprophylaxis probably can be safely discontinued in patients without evidence of active *I. belli* infection who have a sustained increase in the CD4 cell count to levels >200 cells/mm<sup>3</sup> for >6 months after initiation of ART (**BIII**).

## Special Considerations During Pregnancy

TMP-SMX is the agent of choice for primary treatment and secondary prophylaxis in pregnant women, as it is in persons who are not pregnant. Although first-trimester exposure to trimethoprim has been associated with a small increased risk of birth defects,<sup>39-42</sup> TMP-SMX therapy should be provided in the setting of maternal symptomatic *I. belli* infection. Because of concerns about possible teratogenicity associated with first-trimester drug exposure, clinicians may withhold secondary prophylaxis during the first trimester and treat only symptomatic infection (**CIII**). Although pyrimethamine has been associated with birth defects in animals, limited human data have not suggested an increased risk of defects.<sup>43</sup> Human data about the use of ciprofloxacin during several hundred pregnancies have not suggested an increased risk of birth defects or cartilage abnormalities.<sup>44</sup>

## Recommendations for Treating *Isospora belli* Infection

### Treating *Isospora belli* Infection

#### General Management Considerations:

- Fluid and electrolyte support in patients with dehydration (**AIII**)
- Nutritional supplementation for malnourished patients (**AIII**)

#### Preferred Therapy for Acute Infection:

- TMP-SMX (160 mg/800 mg) PO (or IV) QID for 10 days (**AII**), or
- TMP-SMX (160 mg/800 mg) PO (or IV) BID for 7–10 days (**BI**)
- One approach is to start with TMP-SMX (160 mg/800 mg) BID regimen first, and increase daily dose and/or duration (up to 3–4 weeks) if symptoms worsen or persist (**BIII**)
- IV therapy for patients with potential or documented malabsorption

#### Alternative Therapy For Acute Infection (For Patients with Sulfa Intolerance):

- Pyrimethamine 50–75 mg PO daily + leucovorin 10–25 mg PO daily (**BIII**), or
- Ciprofloxacin 500 mg PO BID for 7 days (**CI**)

### Chronic Maintenance Therapy (Secondary Prophylaxis)

(In Patients with CD4 Count  $<200/\text{mm}^3$ )

#### Preferred Therapy:

- TMP-SMX (160 mg/800 mg) PO 3 times weekly (**AI**)

#### Alternative Therapy:

- TMP-SMX (160 mg/800 mg) PO daily (**BIII**), or
- TMP-SMX (320 mg/1600 mg) PO 3 times weekly (**BIII**), or
- Pyrimethamine 25 mg PO daily + leucovorin 5–10 mg PO daily (**BIII**)
- Ciprofloxacin 500 mg PO 3 times weekly (**CI**) as a second line alternative

#### Criteria for Discontinuation of Chronic Maintenance Therapy

- Sustained increase in CD4 count  $>200$  cells/ $\text{mm}^3$  for  $>6$  months in response to ART and without evidence of active *I. belli* infection (**BIII**)

**Key to Acronyms:** ART = antiretroviral therapy; BID = twice daily; IV = intravenous; PO = orally; QID = four times a day; TMP-SMX = trimethoprim-sulfamethoxazole

## References

1. Anglaret X, Chene G, Attia A, et al. Early chemoprophylaxis with trimethoprim-sulphamethoxazole for HIV-1-infected adults in Abidjan, Cote d'Ivoire: a randomised trial. Cotrimo-CI Study Group. *Lancet*. May 1 1999;353(9163):1463-1468. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10232311>.
2. Lindsay DS, Dubey JP, Blagburn BL. Biology of *Isospora* spp. from humans, nonhuman primates, and domestic animals. *Clin Microbiol Rev*. Jan 1997;10(1):19-34. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8993857>.
3. Guiguet M, Furco A, Tattevin P, Costagliola D, Molina JM, French Hospital Database on HIVCEG. HIV-associated *Isospora belli* infection: incidence and risk factors in the French Hospital Database on HIV. *HIV Med*. Mar 2007;8(2):124-130. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17352769>.
4. Sorvillo FJ, Lieb LE, Seidel J, Kerndt P, Turner J, Ash LR. Epidemiology of isosporiasis among persons with acquired immunodeficiency syndrome in Los Angeles County. *Am J Trop Med Hyg*. Dec 1995;53(6):656-659. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8561272>.
5. Certad G, Arenas-Pinto A, Pocaterra L, et al. Isosporiasis in Venezuelan adults infected with human immunodeficiency virus: clinical characterization. *Am J Trop Med Hyg*. Aug 2003;69(2):217-222. Available at <http://www.ncbi.nlm.nih.gov/pubmed/13677379>.
6. DeHovitz JA, Pape JW, Boncy M, Johnson WD, Jr. Clinical manifestations and therapy of *Isospora belli* infection in

patients with the acquired immunodeficiency syndrome. *N Engl J Med*. Jul 10 1986;315(2):87-90. Available at <http://www.ncbi.nlm.nih.gov/pubmed/3487730>.

7. Pape JW, Verdier RI, Johnson WD, Jr. Treatment and prophylaxis of *Isospora belli* infection in patients with the acquired immunodeficiency syndrome. *N Engl J Med*. Apr 20 1989;320(16):1044-1047. Available at <http://www.ncbi.nlm.nih.gov/pubmed/2927483>.
8. Forthal DN, Guest SS. *Isospora belli* enteritis in three homosexual men. *Am J Trop Med Hyg*. Nov 1984;33(6):1060-1064. Available at <http://www.ncbi.nlm.nih.gov/pubmed/6507724>.
9. Modigliani R, Bories C, Le Charpentier Y, et al. Diarrhoea and malabsorption in acquired immune deficiency syndrome: a study of four cases with special emphasis on opportunistic protozoan infestations. *Gut*. Feb 1985;26(2):179-187. Available at <http://www.ncbi.nlm.nih.gov/pubmed/4038492>.
10. Whiteside ME, Barkin JS, May RG, Weiss SD, Fischl MA, MacLeod CL. Enteric coccidiosis among patients with the acquired immunodeficiency syndrome. *Am J Trop Med Hyg*. Nov 1984;33(6):1065-1072. Available at <http://www.ncbi.nlm.nih.gov/pubmed/6334448>.
11. Bialek R, Overkamp D, Rettig I, Knobloch J. Case report: Nitazoxanide treatment failure in chronic isosporiasis. *Am J Trop Med Hyg*. Aug 2001;65(2):94-95. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11508398>.
12. Williams DT, Smith RS, Mallon WK. Severe hypokalemia, paralysis, and AIDS-associated *Isospora belli* diarrhea. *J Emerg Med*. Dec 2011;41(6):e129-132. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18993015>.
13. Benator DA, French AL, Beaudet LM, Levy CS, Orenstein JM. *Isospora belli* infection associated with acalculous cholecystitis in a patient with AIDS. *Ann Intern Med*. Nov 1 1994;121(9):663-664. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7944075>.
14. Lagrange-Xelot M, Porcher R, Sarfati C, et al. Isosporiasis in patients with HIV infection in the highly active antiretroviral therapy era in France. *HIV Med*. Feb 2008;9(2):126-130. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18257775>.
15. Walther Z, Topazian MD. *Isospora* cholangiopathy: case study with histologic characterization and molecular confirmation. *Hum Pathol*. Sep 2009;40(9):1342-1346. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19447468>.
16. Gonzalez-Dominguez J, Roldan R, Villanueva JL, Kindelan JM, Jurado R, Torre-Cisneros J. *Isospora belli* reactive arthritis in a patient with AIDS. *Annals of the rheumatic diseases*. Sep 1994;53(9):618-619. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7979603>.
17. Bialek R, Binder N, Dietz K, Knobloch J, Zelck UE. Comparison of autofluorescence and iodine staining for detection of *Isospora belli* in feces. *Am J Trop Med Hyg*. Sep 2002;67(3):304-305. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12408672>.
18. Frenkel JK, Silva MB, Saldanha J, et al. *Isospora belli* infection: observation of unicellular cysts in mesenteric lymphoid tissues of a Brazilian patient with AIDS and animal inoculation. *The Journal of eukaryotic microbiology*. 2003;50 Suppl:682-684. Available at <http://www.ncbi.nlm.nih.gov/pubmed/14736218>.
19. Restrepo C, Macher AM, Radany EH. Disseminated extraintestinal isosporiasis in a patient with acquired immune deficiency syndrome. *Am J Clin Pathol*. Apr 1987;87(4):536-542. Available at <http://www.ncbi.nlm.nih.gov/pubmed/3826017>.
20. Bernard E, Delgiudice P, Carles M, et al. Disseminated isosporiasis in an AIDS patient. *Eur J Clin Microbiol Infect Dis*. Sep 1997;16(9):699-701. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9352268>.
21. Dillingham RA, Pinkerton R, Leger P, et al. High early mortality in patients with chronic acquired immunodeficiency syndrome diarrhea initiating antiretroviral therapy in Haiti: a case-control study. *Am J Trop Med Hyg*. Jun 2009;80(6):1060-1064. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19478276>.
22. Verdier RI, Fitzgerald DW, Johnson WD, Jr., Pape JW. Trimethoprim-sulfamethoxazole compared with ciprofloxacin for treatment and prophylaxis of *Isospora belli* and *Cyclospora cayetanensis* infection in HIV-infected patients. A randomized, controlled trial. *Ann Intern Med*. Jun 6 2000;132(11):885-888. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10836915>.
23. Guerrant RL, Van Gilder T, Steiner TS, et al. Practice guidelines for the management of infectious diarrhea. *Clin Infect Dis*. Feb 1 2001;32(3):331-351. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11170940>.
24. Mojon M, Coudert J, E.O. dL. Serious isosporosis by *Isospora belli*: a case report treated by Fansidar [Abstract]. *Southeast Asian J Trop Med Public Health*. 12:449-500. 1981.



25. Ebrahimzadeh A, Bottone EJ. Persistent diarrhea caused by *Isospora belli*: therapeutic response to pyrimethamine and sulfadiazine. *Diagn Microbiol Infect Dis*. Oct 1996;26(2):87-89. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8985661>.
26. Trier JS, Moxey PC, Schimmel EM, Robles E. Chronic intestinal coccidiosis in man: intestinal morphology and response to treatment. *Gastroenterology*. May 1974;66(5):923-935. Available at <http://www.ncbi.nlm.nih.gov/pubmed/4826994>.
27. Navin TR, Miller KD, Satriale RF, Lobel HO. Adverse reactions associated with pyrimethamine-sulfadoxine prophylaxis for *Pneumocystis carinii* infections in AIDS. *Lancet*. Jun 8 1985;1(8441):1332. Available at <http://www.ncbi.nlm.nih.gov/pubmed/2860516>.
28. Weiss LM, Perlman DC, Sherman J, Tanowitz H, Wittner M. *Isospora belli* infection: treatment with pyrimethamine. *Ann Intern Med*. Sep 15 1988;109(6):474-475. Available at <http://www.ncbi.nlm.nih.gov/pubmed/3261956>.
29. Jongwutiwes S, Sampatanukul P, Putaporntip C. Recurrent isosporiasis over a decade in an immunocompetent host successfully treated with pyrimethamine. *Scandinavian journal of infectious diseases*. 2002;34(11):859-862. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12578164>.
30. Dionisio D, Sterrantino G, Meli M, Leoncini F, Orsi A, Nicoletti P. Treatment of isosporiasis with combined albendazole and ornidazole in patients with AIDS. *AIDS*. Sep 1996;10(11):1301-1302. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8883600>.
31. Zulu I, Veitch A, Sianongo S, et al. Albendazole chemotherapy for AIDS-related diarrhoea in Zambia--clinical, parasitological and mucosal responses. *Alimentary pharmacology & therapeutics*. 2002; 16(3):595-601. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=11876715](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11876715).
32. Romero Cabello R, Guerrero LR, Munoz Garcia MR, Geyne Cruz A. Nitazoxanide for the treatment of intestinal protozoan and helminthic infections in Mexico. *Trans R Soc Trop Med Hyg*. Nov-Dec 1997;91(6):701-703. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9580117>.
33. Doumbo O, Rossignol JF, Pichard E, et al. Nitazoxanide in the treatment of cryptosporidial diarrhea and other intestinal parasitic infections associated with acquired immunodeficiency syndrome in tropical Africa. *Am J Trop Med Hyg*. Jun 1997;56(6):637-639. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9230795>.
34. Meyohas MC, Capella F, Poirot JL, et al. [Treatment with doxycycline and nifuroxazide of *Isospora belli* infection in AIDS]. *Pathologie-biologie*. Jun 1990;38(5 ( Pt 2)):589-591. Available at <http://www.ncbi.nlm.nih.gov/pubmed/2385457>.
35. Gaska JA, Tietze KJ, Cosgrove EM. Unsuccessful treatment of enteritis due to *Isospora belli* with spiramycin: a case report. *J Infect Dis*. Dec 1985;152(6):1336-1338. Available at <http://www.ncbi.nlm.nih.gov/pubmed/4067332>.
36. Musey KL, Chidiac C, Beaucaire G, Houriez S, Fourrier A. Effectiveness of roxithromycin for treating *Isospora belli* infection. *J Infect Dis*. Sep 1988;158(3):646. Available at <http://www.ncbi.nlm.nih.gov/pubmed/3411149>.
37. Limson-Pobre RN, Merrick S, Gruen D, Soave R. Use of diclazuril for the treatment of isosporiasis in patients with AIDS. *Clin Infect Dis*. Jan 1995;20(1):201-202. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7727660>.
38. Kayembe K, Desmet P, Henry MC, Stoffels P. Diclazuril for *Isospora belli* infection in AIDS. *Lancet*. Jun 17 1989;1(8651):1397-1398. Available at <http://www.ncbi.nlm.nih.gov/pubmed/2567420>.
39. Czeizel AE, Rockenbauer M, Sorensen HT, Olsen J. The teratogenic risk of trimethoprim-sulfonamides: a population based case-control study. *Reprod Toxicol*. Nov-Dec 2001;15(6):637-646. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11738517>.
40. Hernandez-Diaz S, Werler MM, Walker AM, Mitchell AA. Folic acid antagonists during pregnancy and the risk of birth defects. *N Engl J Med*. Nov 30 2000;343(22):1608-1614. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11096168>.
41. Hernandez-Diaz S, Werler MM, Walker AM, Mitchell AA. Neural tube defects in relation to use of folic acid antagonists during pregnancy. *American journal of epidemiology*. May 15 2001;153(10):961-968. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11384952>.
42. Jungmann EM, Mercey D, DeRuiter A, et al. Is first trimester exposure to the combination of antiretroviral therapy and folate antagonists a risk factor for congenital abnormalities? *Sexually transmitted infections*. Dec 2001;77(6):441-443. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11714944>.
43. Deen JL, von Seidlein L, Pinder M, Walraven GE, Greenwood BM. The safety of the combination artesunate and pyrimethamine-sulfadoxine given during pregnancy. *Trans R Soc Trop Med Hyg*. Jul-Aug 2001;95(4):424-428. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11579889>.
44. Nahum GG, Uhl K, Kennedy DL. Antibiotic use in pregnancy and lactation: what is and is not known about teratogenic and toxic risks. *Obstet Gynecol*. May 2006;107(5):1120-1138. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16648419>.